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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/668,508	09/22/2000	Henry E. Young	1304-1-019CIP	1973

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EXAMINER	
TON, THAIAN N	

ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/668,508	YOUNG ET AL.	
	Examiner	Art Unit	
	Thaian N. Ton	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 July 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14-17 and 33-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14-17, 33-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' Amendment and Remarks, filed 7/30/08, have been entered. Claims 14-16, 33-35 are amended; claim 36 is cancelled; claims 14-17 and 33-35 are pending and under current examination.

Claim Rejections - 35 USC § 112 – New Matter

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 14-17 and 33-35 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

37 CFR 1.118 (a) states that "No amendment shall introduce new matter into the disclosure of an application after the filing date of the application".

Applicants have amended the claims to longer recite that the cells do not spontaneously differentiate, remain quiescent in serum-free medium and in the absence of an induction agent. However, the claims 14-17 continue to recite that the stem cells do not form tumors in an animal. Applicants have additionally added this limitation to claims 33-35. As stated in the prior Office action (pages 3-4 of the Office action, mailed 1/28/08). Applicants' amendment is considered new matter because there is no description in the specification for a pluripotent stem cell with the limitations claimed, that does not form tumors in an animal.

Applicants have pointed to p. 3, lines 9-11, p. 8, lines 18-20, p. 36, lines 7-11 and pages 54-55. These citations are directed to the newly filed amendments, but do not provide any support for the phrase that the stem cells do not form tumors in an animal. Applicants have not pointed to support in the as-filed disclosure where this support may be found. Accordingly, this rejection is maintained.

To the extent that the claimed compositions and/or methods are not described in the instant disclosure, claims 14-17 and 33-35 are also rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, since a disclosure cannot teach one to make or use something that has not been described.

MPEP §2163.06 notes:

> *If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. In re Rasmussen, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981).*

MPEP §2163.02 teaches that:

> *Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed...If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application.*

MPEP §2163.06 further notes:

> *When an amendment is filed in reply to an objection or rejection based on 35 U.S.C. 112, first paragraph, a study of the entire application is often necessary to determine whether or not "new matter" is involved. Applicant should therefore specifically point out the support for any amendments made to the disclosure.* (Emphasis added).

Enablement

Claims 14-17 and 33-35 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Applicants' Arguments. Applicants argue that the claims as submitted are enabled. Applicants argue that the instant cells are absolutely distinct from prior art ES cells, and that the full extent of any of the stem cells embryonic-like feature reside in their capability to differentiate to cells of each and any of endodermal, ectodermal and mesodermal lineages, and it is this feature that lead to designating them as "embryonic-like". Applicants argue that the instant stem cells are new, novel and unique from any stem cells, embryonic-like (ES) or otherwise, in the prior art. Applicants argue that by eliminating the term "embryonic-like" enables the claims. Applicants argue that the claims set out characteristics and tests recognized by and available to the skilled artisan to test, establish, verify and uniquely identify the instant stem cells. See pages 7-8 of the Response.

Response to Arguments. These arguments are not persuasive. The claims are directed to isolated *pluripotent* cells. The elimination of the term "embryonic-like" does not overcome the prior rejection of record. In particular, the term *pluripotent* is one of art, which has recognized requirements. For example,

Thomson *et al.* (**PNAS**, 92:7844-7848 (August 1995)) teach the specific, art-recognized characteristics of pluripotent cells - that these cells remain undifferentiated in culture in continuous passage, maintain a normal karyotype, express appropriate cell markers (alkaline phosphatase, SSEA-3, SSEA-4, TRA-160, TRA-1-81) and, when injected into SCID mice, they consistently differentiate into derivatives of all three germ layers. See *Abstract* and p. 7845-7846. The claimed invention requires that the cells be pluripotent, however, the workings examples and evidence of record fail to show that the cells are pluripotent. Applicants' stem cells do not fulfill the criteria set forth by the art of record, with regard to the characterization of the claimed cells such that they would be considered pluripotent. The instant claims state that the stem cells do not form tumors in an animal. Thomson, as well as the art of record, makes clear that the evidence of tumor formation in a SCID mouse shows *in vivo* differentiation capabilities of pluripotent cells. The Examiner further notes that the breadth of the claims recite that the stem cells do not form tumors in an animal -- this includes immunocompetent and immunodeficient animals. There is no evidence of record that Applicants' cells will not form tumors in either immunocompetent or immunodeficient animals, or both. It is clear that the art, with regard to tumor formation, is directed to SCID mice, when characterizing pluripotent cells, such as ES cells.

Additionally, the Examiner reiterates that the characterization Applicants' cells are pluripotent is not predictable, as stated above, and additionally, because the cells express markers fail to uniquely identify embryonic stem cells, because these markers as expressed in other cell types. The Examiner presented these arguments in the prior Office action (see pages 6-9 of the prior Office action). In particular, the cells that the specification teaches expresses markers in EC cells, which are not expressed in ES cells, and further, EC cells are different than ES cells in various ways, including differentiation potential. Additionally, the specification teaches that the cells express alkaline phosphatase, however, this marker fails to

particularly identify a single cell type because this marker is expressed in other cell types (see Pera, Eiges, Gerecht-Nir, cited previously). Similarly, the specification teaches that the claimed cells express SSEA-4 (indicated by MC-813-70). See Table 7. Although SSEA-4 is a marker that is expressed in human ES cells, it is also expressed in mesenchymal stem cells; see Gang (cited previously).

Furthermore, the claims are broadly directed to cells from any species, thus, there is no teaching, with regard to expression markers from cells other than human. Thus, although specification has shown that the claimed cells express alkaline phosphatase and SSEA-4, this does not provide sufficient guidance to show that these cells are pluripotent. The claims do not meet the definitions for a pluripotent cell, as set forth by the cited art above. The elimination of the term "embryonic-like" does not overcome this rejection, because the term "pluripotent" requires the factors that are discussed above and previously to define the cells.

Applicants provide no specific argument with regard to claims 33-35, wherein the cells express SSEA4 and CD10, Applicants are referred to the prior Office actions, which shows that pluripotent cells, such as ES cells, have specific characteristics, including differentiation potential, morphology, as well as specific cell markers, which define these cells. The claims are broadly directed to cells from any species, thus, there is no teaching, with regard to expression markers from cells other than human. CD10 is also expressed in various cell types. Applicants' cells would not be considered pluripotent, because they express markers and have phenotypes and characteristics that fail to establish that they are pluripotent. It is unclear what type of cell(s) are encompassed by Applicants' cells because they do not possess many of the art-recognized characteristics of pluripotent cells. The characterization of a cell as pluripotent not only refers to its differentiation potential, but specific markers that serve to define these cells.

The Amount of Experimentation Necessary. Accordingly, in view of the lack of teachings or guidance provided by the specification, with regard to the

identification and characterization of the claimed cells, the state of the art, which clearly shows that using particular markers fails to establish or uniquely identify Applicants' cells, it would have required undue experimentation for one of ordinary skill in the art to make and use the claimed cells.

Written Description

Claims 14-17 and 33-35 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicants' Arguments. Applicants argue that the instant claims, provide identification and characterization to establish and uniquely identify the instant stem cells and that the claims set out characteristics and tests recognized by and available to the skilled artisan to establish, verify and uniquely identify the instant stem cells. See pages 8-9 of the Response.

Response to Arguments. Applicants' arguments have been fully considered, but are not persuasive. In particular, the Examiner set forth in the prior Office action that the markers that are used to identify the instant pluripotent stem cells fail to be sufficiently described such that one of skill in the art could recognize and identify these cells. The Examiner notes that Table 7 teaches differential expression markers of EC cells, and alkaline phosphatase, as well as SSEA-4 in conditions that include insulin and dexamethasone for the CF-NHDF2 cell line. Table 8 shows that the cells, after 37 doublings, do not express alkaline phosphatase, but at 40 doublings, express alkaline phosphatase, and after 45 doublings, no expression of alkaline phosphatase is noted. Cell line CM-SKM2 did not show any expression of alkaline phosphatase or SSEA-4 (Table 10). As shown in prior Office actions and above, these markers are expressed in pluripotent cells,

but not uniquely. Thus, it is unclear from Applicants' results what markers are expressed (or not) in the claimed cells, such that one of skill in the art could readily identify that Applicants had possession of the claimed cells. Specifically, the specification fails to describe the markers and specific characterization of the cells (such as teratoma formation), and the skilled artisan, although recognizing that specific markers and characteristics identify pluripotent cells, could not envision which of such markers or characteristics, would uniquely identify Applicants' claimed cells. Accordingly, the rejection is maintained.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 14-17 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 14, 15 remain unclear.

1. Applicants argue that the term "not totipotent" has been deleted from the claims (see p. 9 of the Response). However, the claims retain this language. The claims are already limited to "pluripotent" cells. Pluripotent cells are not totipotent cells, they are not capable of producing extraembryonic tissues, and do not fulfill the definition of "totipotent". Thus, recitation that the cells are "not totipotent" does not limit the claim further.

Claims 16-17 depend from claim 15.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 14-17 stand rejected under 35 U.S.C. 103(a) being unpatentable over Shamblott when taken with Sambrook *et al.*

Applicants' Arguments. Applicants argue that their cells are distinguished from the cells of Shamblott. Applicants argue that the Examiner seems to be requesting a specific cell marker for distinction, and that Applicants argue that the cells have been and can be distinguished from one another by any various characters, activities and functions. Applicants argue that although cell markers are one way to distinguish cells, there are other characteristics that are possible and suitable for distinction. Applicants argue that ES and EG cells have a disorganized and heterogeneous nature of development in culture, forming EBs, which are aggregates of cells, when these cells are implanted into animals or presented subcutaneously they form teratomas or tumors containing derivatives of all three germ layers. Applicants' pluripotent cells do not form tumors in animals, and additionally, this disorganized nature of ES/EG cells makes them impossible to manipulate into a specified lineage or to multiple separate lineages and thereby are not capable of incorporation into the existing tissue because of their heterogeneous, unpredictable and teratogenic character. Applicants argue that the instantly claimed stem cells do not have these characteristics.

Response to Arguments. Applicants' arguments and amendments are not found to be persuasive. The heterogeneous nature to which Applicants' are referring to is directed to spontaneous differentiation of ES/EG cells to form EBs. That is, when the cells are allowed to pile up and form EBs. However, given specific

differentiation factors, ES cells can be directed to differentiate into a particular cell type of interest. Similarly, Applicants' cells require differentiation agents to direct the differentiation of the cells into a particular cell type. There is nothing in the art or evidence of record that suggests that ES cells cannot and do not commit to multiple separate lineages and can incorporate into existing tissues. Applicants' arguments are only directed to EBs, and not directed differentiation of ES cells. Applicants' arguments do not distinguish the instantly claimed cells from those of Shamblott. The instantly claimed cells are pluripotent stem cells, as are Shamblott's cells. Additionally, the Examiner noted in the prior Office action that Shamblott's cells do not form teratomas (p. 13 of the prior Office action). Applicants' arguments with regard to ES/EG cells' heterogeneous nature in forming EBs is with respect to the differentiation of ES/EG cells. That is, a differentiated cell would no longer be considered pluripotent. The claims are directed to pluripotent cells, not differentiated cells. The amendments to the claims do not overcome the prior rejection of record, because the cells as taught by Shamblott fulfill the limitations of the claims. The Examiner is not requiring a particular marker to overcome the art rejection, as suggested by Applicants. The Examiner has clearly pointed out that pluripotent cells have art-recognized characteristics (see prior Office action) and Applicants' amendment to the claims has not provided any discernable characteristics from the claimed cells and that of Shamblott, the prior rejection is maintained.

Shamblott *et al.* teach the generation of human pluripotent stem cells from gonadal ridges and mesenteries containing primordial germ cells [PGCs] and teach that embryoid bodies collected from these cultures revealed a wide variety of differentiated cell types, including derivatives of all three embryonic germ layers [see *Abstract*]. In particular, Shamblott *et al.* teach that gonadal ridges and mesenteries of 5 to 9 week old human fetuses and cells initially cultured on a layer of mouse STO fibroblast feeder layer. The cells formed embryoid bodies, which were

collected and analyzed immunohistochemically [see pp. 13726-13727, *Materials & Methods*]. It was found that the embryoid bodies demonstrated derivatives of the three embryonic germ layers [see p. 13729, 2nd column and Table 1]. Note that Shamblott teach the pluripotent embryonic-like stem cells because the claims do not provide any requisite characteristics (*e.g.*, specific markers, etc.) of the claimed embryonic-like stem cells such that they would be distinguished from the cells taught by Shamblott. Further, the method claim has been included in this rejection because the cells as instantly claimed are not distinguishable from those taught in the art. The cells as taught by Shamblott fulfill the requirements of the claims because they are capable of differentiation to cells of each and any of endodermal, ectodermal and mesodermal lineages, and are capable of self-renewal.

Shamblott do not teach the transfection of the pluripotent stem cells to produce a genetically engineered pluripotent stem cell. However, prior to the time of the claimed invention, Sambrook teach methods of transfecting mammalian cells with any gene of interest [see 16.33-16.38]. Accordingly, in view of the combined teachings of Shamblott and Sambrook, it would have been obvious for one of ordinary skill in the art at the time the claimed invention was made, to use the PGCs, as taught by Shamblott and transfect them with any DNA of interest, with a reasonable expectation of success. One of skill in the art would have been sufficiently motivated to make such a modification, as expression of proteins in mammalian cells can provide different purposes, as described by Sambrook on p. 16.3, such as for the expression of large amounts of protein of biological interest, or to study the biosynthesis and intracellular transport of proteins following their expression in various cell types.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Thaian N. Ton whose telephone number is (571)272-0736. The examiner can normally be reached on 9-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Thaian N. Ton/
Primary Examiner, Art Unit 1632